Center for Drug Evaluation and Research

Bioresearch Monitoring

NOTE: The Warning Letters summarized below were chosen to provide examples of the types of Warning Letters issued for violations of FDA regulations governing the conduct of clinical trials. A complete list of Warning Letters issued under FDA's Bioresearch Monitoring Program is available on FDA's Website at: http://www.fda.gov/foi/warning.htm.

Failure to Adhere to FDA Regulations Results in Warning Letter to Foreign Investigator

On August 10, 2006, FDA's Center for Drug Evaluation and Research (CDER) Division of Scientific Investigations (DSI), Office of Compliance, issued a Warning Letter to Professor Olga D. Ostroumova, Moscow, Russia. This Warning Letter was one of the first Warning Letters issued by CDER to a clinical investigator conducting research at a site outside the U.S.

The inspection was performed by an FDA investigator, accompanied by a DSI Medical Officer, to review Professor Ostroumova's conduct of a clinical investigation in support of a New Drug Application (NDA) supplement. The study was conducted under a U.S. Investigational New Drug Application, and thus was subject to the U.S. Code of Federal Regulations (CFR).

Based on CDER's evaluation of the inspection report, the documents submitted with the report, and Professor Ostroumova's response to the list of Inspectional Observations, Form FDA 483, CDER concluded that Professor Ostroumova did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

The following is a listing of the major violations noted during the inspection:

- Failure to maintain adequate and accurate case histories that record all observations and data pertinent to the investigation;
- Failure to maintain adequate records of the disposition of the drug including dates, quantity and use by subjects.

The Warning Letter notes that two subjects had identical ECGs at Visit 1 and Visit 4 that were hand dated with different dates.

The Warning Letter stated [in part] the following:

> "In your response letter of March 22, 2006, you stated that both subjects requested copies of their Visit 1 ECGs and that copies were made but which were stored with the study record instead of being given to the subjects but then at Visit 4, these same subjects were mistakenly given copies of their Visit 4 ECGs instead of their Visit 1 ECGs. Your explanation does not adequately explain why each subject had identical ECGs at Visit 1 and Visit 4 that were hand dated with different dates."

The full text of the Warning Letter is available online at: http://www.fda.gov/foi/warning_letters/g6044d.htm

Clinical Investigator Receives Warning for Failure to Maintain Records

Failure to Retain Records of Clinical Study Made it "...impossible for FDA to Verify the Integrity of the Data.."

On November 7, 2006, FDA's Center for Drug Evaluation and Research (CDER) Division of Scientific Investigations (DSI), Office of Compliance, issued a Warning Letter to clinical investigator Dr. Phillip Schworer of Florence, Kentucky.

This inspection was conducted by an FDA field investigator as part of a data audit of clinical studies submitted in support of a New Drug Application (NDA) for a new molecular entity.

Based on CDER's evaluation of the inspection report and the documents submitted with the report, CDER concluded that Dr. Schworer did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

Specifically, the clinical investigator failed to retain records required to be maintained under 21 CFR 312.62(c). This failure to retain records of this clinical study made it impossible for FDA to verify the integrity of the data and to verify that there was adequate protection

of the rights, welfare, and safety of the subjects who participated in the study.

Warning Letter Issued for Failure to Adequately Supervise Clinical Investigation

Clinical Investigator Fails to Maintain Adequate Case Histories Pertinent to Clinical Study

On November 3, 2006, FDA's Center for Drug Evaluation and Research (CDER) Division of Scientific Investigations (DSI), Office of Compliance, issued a Warning Letter to clinical investigator Dr. E. Clinton Lawrence of Atlanta, Georgia.

This inspection was conducted by an FDA field investigator as part of a data audit of clinical studies submitted in support of a New Drug Application (NDA).

Based on CDER's evaluation of the inspection report and the documents submitted with the report, CDER concluded that Dr. Lawrence did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

After the review of all submitted information, the investigation found that Dr. Lawrence:

- Failed to personally conduct or supervise the clinical investigation [21 CFR 312.60];
- Failed to ensure that the investigation was conducted according to the investigator statement, investigational plan, and applicable regulations [21 CFR 312.60];
- Failed to maintain adequate records of the disposition of the drug including dates, quantity and use by subjects [21 CFR 312.62(a)];
- Failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation [21 CFR 312.62(b)]; and
- Failed to promptly report to the IRB all unanticipated problems involving risks to human subjects or others [21 CFR 312.66].

Failure to Adhere to FDA Regulations in Clinical Investigations Results in Warning Letter

On October 27, 2005, FDA's Center for Drug Evaluation and Research (CDER) Division of Scientific Investigations, Office of Medical Policy, issued a Warning Letter to Spencer B. Jones, M.D., Salt Lake City, Utah. An FDA investigator conducted an investigation

to review Dr. Jones' conduct of certain clinical investigations.

This inspection was conducted as part of FDA's Bioresearch Monitoring Program, which includes inspections designed to monitor the conduct of research and to ensure that the rights, safety and welfare of the human subjects of those studies have been protected.

Based on CDER's evaluation of the inspection report, the documents submitted with the report, an affidavit signed by Dr. Jones, and Dr. Jones' response to Form FDA 483, CDER concluded that Dr. Jones did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

The following is a listing of the major violations noted during the inspection:

- Failure to protect the rights, safety, and welfare of subjects under Dr. Jones' care;
- Failure to ensure that the investigation was conducted according to the investigational plan;
- Failure to promptly report to the Institutional Review Board (IRB) all changes in research activity;
- Failure to ensure that no changes were made in the research without IRB approval;
- Failure to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug; and,
- Failure to obtain informed consent in accordance with 21 CFR Part 50 from each human subject to whom the investigational drug was administered.

The full text of the Warning Letter is available online at: http://www.fda.gov/foi/warning_letters/g5569d.htm.

Investigational Review Board Receives Warning Letter

On January 26, 2006, FDA issued a Warning Letter to the Chairman of the Human Investigation Committee, Houston, Texas. Investigators representing FDA inspected the Human Investigation Committee (HIC) of Houston, Texas, which serves as an Institutional Review Board (IRB).

The purpose of this inspection was to determine whether HIC was in compliance with federal laws and regulations governing IRBs and

regulations governing the protection of human subjects participating in clinical trials.

Based on CDER's evaluation of the establishment inspection report, the documents submitted with that report, and the Chairman's written response, FDA concluded that the IRB failed to adhere to certain requirements in 21 CFR Parts 56 and 50 (as described below). The regulatory violations were identified from FDA's review of the IRB's procedures and a review of certain studies.

The Warning Letter emphasized the following violations:

- Failure of the IRB to ensure that informed consent would be sought from each prospective subject or the subject's legally authorized representative in accordance with and to the extent required by 21 CFR Part 50;

- Failure of the IRB to ensure that risks to subjects were minimized by using procedures consistent with sound research design and which do not unnecessarily expose subjects to risk;

- Failure of the IRB to have a written procedure in place to ensure prompt reporting to FDA of any unanticipated problems involving risks to human subjects or others.

The full text of the Warning Letter is available online at:
http://www.fda.gov/foi/warning_letters/g5700d.htm

Counterfeit Drugs

FDA Warns Consumers Not to Buy or Use Rx Drugs from Various Canadian Websites

On August 30, 2006, FDA issued a Press Release advising consumers not to purchase prescription drugs from websites that have orders filled by Mediplan Prescription Plus Pharmacy or Mediplan Global Health in Manitoba, Canada, following reports of counterfeit versions of prescription drug products being sold by these companies to U.S. consumers.

FDA recommended that consumers who purchased drugs from these websites not use the products because they may be unsafe. Preliminary laboratory results found counterfeits of the following drug products from these websites: Lipitor, Diovan, Actonel, Nexium, Hyzaar, Ezetrol (known as Zetia in the United States), Crestor, Celebrex, Arimidex, and Propecia. All of these medications require a prescription from a licensed health care provider to be legally dispensed.

DRUG NAME	USE(S)
LIPITOR	Cholesterol disorders

CRESTOR	Cholesterol disorders
ZETIA (US name) / EZETROL (Canadian name)	Cholesterol disorders
DIOVAN	High blood pressure
HYZAAR	High blood pressure
ACTONEL	Osteoporosis in postmenopausal women
NEXIUM	Gastroesophageal reflux disease (GERD)
CELEBREX	Arthritis-related pain
ARIMIDEX	Breast cancer
PROPECIA	Male-pattern baldness

As a general matter, FDA advises consumers to use caution when buying medical products online. Although a website may appear reputable and similar to legitimate retail pharmacy websites, many actually operate from outside the U.S. and provide unapproved drugs from unreliable sources.

For example, in August of 2005, FDA conducted an operation at New York,

Miami, and Los Angeles airports. This investigation found that nearly half of the imported drugs that FDA intercepted were from four selected countries.

These imported drugs were shipped to fill orders that consumers believed they were placing with "Canadian pharmacies." Of the drugs being promoted as "Canadian," based on accompanying documentation, 85 percent actually came from 27 other countries around the globe. A number of these products also were found to be counterfeit. These results demonstrated that some Internet sites that claimed to be "Canadian" were, in fact, selling drugs of dubious origin, safety and efficacy.

FDA's announcement is consistent with FDA's earlier message of the dangers posed by such websites and the need for caution on behalf of the public. Drug counterfeiting defrauds consumers and can expose them to products containing unknown, ineffective, or harmful ingredients.

Counterfeit drugs may be toxic or contain doses that are too small to treat a medical condition, or so large that they could endanger the health of the user. Because of the dangers posed by counterfeit drugs, FDA aggressively investigates all instances of drug counterfeiting.

Good Manufacturing Practices

Active Pharmaceutical Ingredients

Nationwide Recall of Active Pharmaceutical Ingredient Tacrolimus

Firm Initiates Nationwide Recall of Tacrolimus After Learning Some Lots Were Sub-potent

On May 11, 2006, Spectrum Laboratory Products, Inc, (Spectrum), Gardena,California, announced that the firm was initiating a voluntary nationwide recall of the active pharmaceutical ingredient (API) tacrolimus after learning some lots were sub-potent. Tacrolimus is an immunosuppressive drug used to prevent rejection of transplanted solid organs such as heart or kidney. The blood levels of tacrolimus in some patients were significantly lower than would be expected based solely on the lower assay results.

The use of sub-potent tacrolimus in compounded drugs for transplant recipients may lead to sub-therapeutic tacrolimus blood levels and an unacceptably increased risk of solid organ transplant rejection. At least one injury was reported.

Tacrolimus is identified as Catalog Number T3192. Recalled lots included the following: TA1210, UD1060, UF0298, UL0964, VB0031.

Spectrum tacrolimus API has been used by pharmacies for compounding purposes. The firm advised that patients receiving tacrolimus for solid organ transplant should not stop taking their medication, but rather should check with their physician or pharmacist. This recall did not apply to tacrolimus marketed in finished dosage form as Prograf® (Astellas Pharma, US) or to Prograf® oral capsules that had been used for compounding.

Spectrum advised pharmacies that had used the Spectrum tacrolimus API that was recalled to stop using it and contact Spectrum to make arrangements to return it. Tacrolimus API was distributed to pharmacies, one university (1 bottle), and one pharmacy distributor (2 bottles) for use in compounding. It can be identified by catalog number T3192 and the name "Tacrolimus" on the label.

Spectrum notified its distributors and customers by telephone and recall letter and arranged for return of all recalled products.

The full text of the Press Release is available online at: http://www.fda.gov/oc/po/firmrecalls/spectrum05_06.html.

Finished Pharmaceuticals

Consent Decrees

Consent Decree of Permanent Injunction
Syntho Pharmaceuticals, Inc./
Intermax Pharmaceuticals, Inc.

Consent Decree Requires Firm to Stop Manufacturing and Recall All Unapproved Drugs and Drugs Manufactured with Poor CGMPs

On August 15, 2006, U.S. District Judge Joseph Bianco entered a Consent Decree of Permanent Injunction against Syntho Pharmaceuticals, Inc., Intermax Pharmaceuticals, Inc., of Farmingdale, New York, and the companies' two co-owners ("the defendants"). The firms manufactured a variety of prescription drugs including: Syntest Tablets - an Rx hormone replacement containing esterified estrogens and methyl testosterone; Coldec Tablets, Coldec D Tablets, Coldec TR Tablets, Dyphylline & Guaifenesin Tablets, USP, Guaidex PD Tablets, Guarded D Tablets, and Crantex LA Tablets - cough/cold medications; Migrazone Capsules - an analgesic/mild sedative, and Usept Tablets - an antiseptic for urinary tract infections.

Syntho/Intermax manufactured and distributed drugs that lacked required FDA approval. Manufacturing problems at the firms included releasing products for distribution that did not meet specifications. Under the consent decree, Syntho/Intermax must stop manufacturing and distributing drugs until FDA determines that the firms fully comply with the CGMP requirements. The firms are also prohibited from marketing drug products that lack necessary FDA approval.

In addition, to ensure that Syntho/Intermax's products already in distribution are no longer used by consumers, FDA requested that Syntho/Intermax recall all unapproved drugs and drugs that they have manufactured and distributed with poor manufacturing standards. FDA advised consumers who had used these firms' products and had concerns or questions to contact their physician or health care practitioner.

Under the Decree, the defendants are required to retain an auditor to conduct inspections of their facilities for a period of five years and provide reports to FDA analyzing the defendants' compliance with CGMPs. The Decree also requires the defendants to cease manufacturing unapproved new drugs. Further, the decree provides for FDA to require recall or shutdown in the event of future violations.

Consent Decree of Permanent Injunction
C. R. Canfield Co., Inc.

FDA Finds Evidence Firm Was Manufacturing Adulterated and Unapproved Drugs

On September 18, 2006, U.S. District Judge Richard H. Kyle entered a Consent Decree of Permanent Injunction against C. R. Canfield Co., Inc. ("Canfield"), and the company's owner ("the defendants"). Pursuant to the decree, the defendants agreed to stop directly or indirectly manufacturing, processing, packing, labeling, holding, or distributing drugs until they provide assurance, to FDA's satisfaction, that: (1) their drug manufacturing operations are in compliance with current good manufacturing practice ("CGMP") requirements; (2) their drug products comply with the drug approval provisions of the FD&C Act; and (3) they ensure that their drug products have adequate directions for use.

The products in question are all used in the practice of dentistry and FDA advised dental professionals and consumers to stop using and discard any product from this manufacturer. FDA also advised that consumers who used this firm's products and had concerns or questions should contact their dental practitioner.

FDA obtained evidence that Canfield manufactured and distributed adulterated and unapproved drugs, including D.S. Dressing (20% Eugenol), D.S. Mini-Dressing (20% Eugenol), D.S. Syringe (20% Eugenol), and D.S. Ointment (20% Eugenol). Canfield promoted these products for the treatment of "dry socket," a condition in which the socket does not heal properly following the extraction of a tooth. The products were available nationwide through dental practices for use by dentists and consumers.

Under the Decree, the defendants are required to retain an auditor to conduct inspections of their facilities for a period of five years and provide reports to FDA analyzing the defendants' compliance with CGMPs. Further, the Decree provides for FDA to require recall or shutdown in the event of future violations.

In September 2004, FDA issued C.R. Canfield Co., Inc., a Warning Letter advising the firm that their three products intended for the treatment of dry socket syndrome were considered unapproved "new" drugs because the firm had not submitted their products for FDA approval. In addition, the products were also misbranded. The Warning Letter also noted that FDA inspections in October 2002 and May 2004 revealed deficiencies in the firm's compliance with CGMPs.

Warning Letter Issued for CGMP Violations, Unapproved New and Misbranded OTC Drugs

On May 31, 2006, FDA's New Jersey District Office issued a Warning Letter to the President and CEO of Neil Laboratories, Inc., East Windsor, New Jersey. An FDA investigator conducted an inspection from December 13 through December 28, 2005, of this drug manufacturing facility located in East

Windsor, New Jersey. During the inspection, an FDA investigator documented deviations from the Current Good Manufacturing Practice (CGMP) regulations.

In addition, the inspection disclosed that the firm manufactured a number of prescription drugs without approved applications. Lastly, several of the over-the-counter (OTC) drugs that the firm manufactured lacked required warnings or other information on their labels.

Warning Letter Issued for Poor CGMPs

On May 31, 2006, FDA's New Jersey District issued a Warning Letter to the President/CEO of Neil Laboratories, Inc., East Windsor, New Jersey. The Warning Letter was issued based on documented deviations from the Current Good Manufacturing Practice (CGMP) regulations observed during a December 13 through December 28, 2005, inspection of this drug manufacturing facility. These deviations from FDA regulations caused the firm's finished drug products to be adulterated and misbranded.

The inspection also documented that the firm manufactured a number of prescription drugs without approved applications. Lastly, several of the over-the-counter drugs that the firm manufactured lacked required warnings or other information on their labels, making them misbranded drugs.

CGMP Deviations

The following are examples of some of the significant CGMP deviations that were found during FDA's inspection:

- Failure to establish scientifically sound and appropriate specifications, standards, sampling plans and test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality, and purity;

- Failure to establish a written testing program designed to assess the stability characteristics of drug products, including reliable, meaningful, and specific test methods putting into question the ability of the product to maintain its labeled strength and characteristics through its expiration date; and,

- Failure to employ appropriate controls over computer or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel.

Unapproved New Prescription Drugs.

The Warning Letter advised Neil Laboratories that FDA regards the firm's products, with descriptions such as "sustained-release," "extended release," and "long acting," as timed release dosage

forms. These products are, therefore, new drugs pursuant to 21 CFR § 310.502(a)(14).

The Act requires that any new drug be the subject of an FDA-approved application before it is introduced into interstate commerce. Neil Laboratories had no approved applications on file for the above products. Therefore, their continued marketing of these products is in violation of the Act.

In addition, these drugs are misbranded because their labeling fails to bear adequate directions for use. Adequate directions cannot be written for prescription drugs so that a layman can use these products safely for their intended uses.

Misbranded Over-the-Counter Drugs

The Warning Letter also noted that Neil Laboratories manufactures numerous drug products for over-the-counter (OTC) use. Some of these OTC drugs are misbranded. Specifically, several aspirin products that the firm manufactures failed to bear the complete Reye's Syndrome warning and the specific pregnancy warning required for products that contain aspirin. Further, certain of the firm's products failed to bear an adequate labeling statement regarding the tamper-evident packaging feature used.

The full text of the Warning Letter, including the firm's responses, is available online at: http://www.fda.gov/foi/warning_letters/g5878d.htm.

FDA Requests Recall of Product Containing Endotoxins

On February 13, 2006, FDA sent a letter to Cytosol Laboratories, Inc., of Braintree, Massachusetts, to request a recall of all brands and sizes of the firm's Balanced Salt Solution (BSS). BSS is a drug used by health professionals to irrigate a patient's eyes, ears, nose and/or throat during a variety of surgical procedures including cataract surgery.

FDA requested the recall because product lots were found to have elevated levels of endotoxin. Endotoxins, also known as pyrogens, are substances found in certain bacteria that cause a wide variety of serious reactions such as fever, shock, changes in blood pressure and other circulatory

An FDA-requested Recall is Initiated to Protect the Public Health When a Product that Has Been Distributed Represents a Risk of Illness or Injury and the Firm Has not Initiated a Recall of the Product

functions. FDA received reports of a serious and potentially irreversible eye injury called Toxic Anterior Segment Syndrome (TASS), which occurs when a contaminant, such as endotoxin, enters the anterior segment of the eye during surgery and causes an inflammatory reaction. FDA received complaints relating to injuries in over 300 patients who were given BSS manufactured by Cytosol Laboratories, Inc.

FDA requested that the company take immediate action to retrieve all inventories of the product, including any existing stock at physician offices and hospitals. FDA instructed hospitals, physicians, and consumers to immediately stop using any of these products, quarantine any remaining product, and if no return instructions from Cytosol were received, destroy the product.

- An estimated one million units of BSS products were distributed between December 2003 and December 2005. The BSS products subject to the recall order were manufactured by Cytosol Laboratories, Inc., for distribution under three labels:
  - "AMO Endosol" distributed by Advanced Medical Optics, Inc. (AMO), Santa Ana, CA;
  - "Cytosol Ophthalmics" distributed by Cytosol Ophthalmics, Lenoir, NC; and
  - "Akorn" distributed by Akorn, Inc., Buffalo Grove, IL.

The full text of the Press Release is available online at: http://www.fda.gov/bbs/topics/news/2006/NEW01315.html.

Firm Issues Nationwide Recall of Cefazolin for Injection

On February 24, 2006, Hanford Pharmaceuticals, Inc., of Syracuse, New York, issued a voluntary recall of four lots (379,975 vials) of Cefazolin for Injection, USP, 1 g/10 mL vials. Cefazolin for Injection, USP, is an antibiotic used in a hospital environment. Certain lots of the active ingredient used to manufacture the product were shown to contain microbial contamination (*Bacillus pumilus*, *Staphylococcus hominis*, *Propionibacterium acnes*, or *Micrococcus luteus*). This microbial contamination could pose a serious or life-threatening risk for some patients. Cefazolin for Injection, USP, is used to treat skin and skin structure, respiratory and other infections.

The firm notified its customers and users of the recall by letter, and asked that they stop distribution, recall from their accounts, and requested the return of the recalled lots. Hospitals, clinics, and users were advised to stop using the affected lots immediately. The letter advised that the product was distributed by Sandoz, Inc., of Broomfield, Colorado, and Watson Pharmaceuticals, Inc. of Corona, California.

Hanford Pharmaceuticals advised customers to check the lot numbers on the product label and promptly return any with the following lot numbers: Sandoz product - C4650, C4537; Watson product - C4689, C4665**.**

The full text of the Press Release is available on line at: http://www.fda.gov/oc/po/firmrecalls/hanford02_06.html.

Nationwide Recall of Injectable Methotrexate

Ethylene Glycol Found in One Lot of Injectable Methotrexate

On December 8, 2005, Bedford Laboratories, a division of Ben Venue Laboratories, Inc., Bedford, Ohio, announced that it was voluntarily recalling one lot of Methotrexate for Injection (preservative free), USP 1 gram per vial (NDC 55390-143-01), Lot# 859142, exp 09/07. Bedford Laboratories initiated the recall after the firm was informed by the manufacturer of the Methotrexate USP active pharmaceutical ingredient (API) that the API used to manufacture Lot # 859142, contained low levels of ethylene glycol.

Human use of preservative-free Methotrexate formulations for intrathecal administration containing ethylene glycol is not permissible.

Bedford Laboratories worked with FDA on this recall. No serious health or safety reports were reported that could be attributed to this situation.

The prescription product was distributed throughout the U.S. in October and November 2005, to wholesalers and distributors, who further distributed the product to hospitals. Customers who had any vials of this one lot of Methotrexate for Injection were instructed to discontinue distribution and use of this lot immediately and contact Bedford Laboratories Customer Service Department. Bedford Laboratories supplies U.S. and International markets with multisource and specialty inject - able products.

The full text of the Press Release for this recall is available online at: http://www.fda.gov/oc/po/firmrecalls/bedford12_05.html.

FDA Issues Public Health Advisory Regarding Ketek Tablets

On January 20, 2006, an article published in the *Annals of Internal Medicine* reported three patients who experienced serious liver toxicity following administration of Ketek (telithromycin). These cases were also reported to FDA's MedWatch.

Telithromycin is marketed and used extensively in many other countries, including countries in Europe and Japan. While it is difficult to determine the actual frequency of adverse events from voluntary reporting systems such as the MedWatch program, FDA continues to evaluate the issue of liver problems in association with use of telithromycin. As a part of this effort, FDA is continuing to work to understand better the frequency of liver-related adverse events reported or approved antibiotics, including telithromycin.

The case review in the online publication by *Annals of Internal Medicine* reported three serious adverse events following administration of telithromycin. All three patients developed jaundice and abnormal liver function. One patient recovered, one required a transplant, and one died. When the livers of the latter two patients were examined in the laboratory, they showed massive tissue death. Two patients had reported some alcohol use. All three patients had previously been healthy and were not using other prescription drugs. FDA is also aware that these patients were all treated by physicians in the same geographic area.

Update:

On June 29, 2006, FDA notified healthcare professionals and patients that it completed its safety assessment of Ketek (telithromycin). FDA determined that additional warnings about the risk of liver toxicity are required and the manufacturer has revised the drug labeling to address this safety concern. In addition, the WARNINGS for patients with myasthenia gravis are being strengthened.

In pre-marketing clinical studies, including a large safety trial and data from other countries, the occurrence of liver problems was infrequent and usually reversible. Based on the pre-marketing clinical data, it appeared that the risk of liver injury with telithromycin was similar to that of other marketed antibiotics. Nonetheless, the product label advises doctors about the potential for liver-related adverse events associated with the use of telithromycin.

Telithromycin is an antibiotic of the ketolide class. It was the first antibiotic of this class to be approved by FDA in April 2004 for the treatment of respiratory infections in adults caused by several types of susceptible microorganisms including *Streptococcus pneumoniae* and *Haemophilus influenzae*.

An FDA Fact Sheet is available online regarding Ketek at: http://www.fda.gov/cder/drug/infopage/telithromycin/default.htm.

In addition, an FDA Patient Information Guide is also available online at: http://www.fda.gov/cder/drug/InfoSheets/patient/telithromycinPIS.HTM.

Importation of Prescription Drugs

Consent Decree of Permanent Injunction Canada Care Drugs, Inc.

On March 9, 2006, the United States District Court for the Southern District of New York entered a Consent Decree of Permanent Injunction against Canada Care Drugs, Inc. (Canada Care), in Goshen, New York, and its owners Christine and Claire Ruggiero. Canada Care had been receiving payments for helping U.S. citizens to illegally import prescription drugs from Canada. The decree permanently shut down Canada Care and enjoined the Ruggieros from illegally importing prescription drugs. The decree also required the Ruggieros to disgorge illegal profits earned while the firm was in operation.

The decree is the result of a legal process that started on November 9, 2004, when the federal government filed a civil complaint against these defendants based on an FDA investigation of Canada Care's illegal importation operations. Canada Care was an affiliate of Rx Depot and Rx of Canada, two firms against which FDA also obtained a consent decree on August 20, 2004.

Medications purchased outside the consumer safety protections built into the U.S. drug distribution system are a public health concern because patients cannot be sure of the quality or the safety and effectiveness of such drugs. Previous FDA investigations found that drugs purchased under these conditions are more likely than FDA-approved drugs to be contaminated, counterfeit, inherently ineffective, or contain different amounts of the active ingredients.

In addition, these products often purport to come from one country, such as Canada, when in fact they come from another. The drugs are often shipped with inadequate instructions for use or inappropriate quantities that facilitate use of the product without the input of a physician, which is necessary to assure that the product is used in a manner to prevent serious, and even fatal, consequences.

The full text of the Press Release is available online at: http://www.fda.gov/bbs/topics/NEWS/2006/NEW01345.html.

Over-the-Counter Products

Consent Decree of Permanent Injunction

Z. Cosmetica, LLC.

On July 27, 2006, the United States District Court for the Eastern District of New York entered a Consent Decree of Permanent Injunction against Z. Cosmetica USA, LLC and its president, Philip J. Zellner. The consent decree permanently enjoins the defendants from manufacturing, holding, or distributing drugs at their facility. The decree also requires the defendants to destroy, under FDA supervision their existing stock of over-the-counter (OTC) drug products and the components.

The defendants are also enjoined from using third-party contractors to manufacture or distribute their drug products unless they first obtain FDA's approval and implement a system for obtaining certifications of compliance with CGMP and any applicable OTC drug monographs from each of their third-party contractors.

In addition, the defendants are required to submit to FDA on a quarterly basis the names of all third-party contractors employed by the firm and lists of all drugs manufactured or distributed by such contractors on the defendants' behalf.

Consent Decree of Permanent Injunction MBI Distributing, Inc.

Poor Manufacturing Calls into Question the Safety of the Firm's Eye Drops

On January 4, 2006, the United States District Court for the Eastern District of California entered a Consent Decree of Permanent Injunction against MBI Distributing, Inc. (MBI), also known as Molecular Biologics, a manufacturer of eye drops and other over-the-counter (OTC) drugs. The decree required the firm to cease manufacturing and distributing drugs until it corrected manufacturing deficiencies and other violations at its Benicia, California facility.

MBI's product line includes eye drops sold under the brand names Oxydrops, Bright Eyes, Bright Eyes II, Clarity Vision for Life, Visitein, and Can-C, as well as several OTC pain relieving drugs. These products are sold by retailers nationwide.

This action was a result of FDA's determination that the firm had been manufacturing eye drops in a manner that did not conform to FDA's current good manufacturing practice requirements. The firm failed to correct violations noted during inspections, despite Agency efforts to have the company achieve compliance. Among other problems, at FDA's most recent inspection, the firm lacked manufacturing controls to ensure that its eye drops were sterile.

FDA also determined that the firm was manufacturing and distributing unapproved new drugs, the eye drop brands Visitein and Clarity Vision for Life, in violation of the Act. In addition, three of the firm's OTC pain relieving drugs, Biogesic, Bio-Ice, and Bio-Heat,

were misbranded in violation of the Act because they did not provide adequate warnings for their safe use.

Under the terms of the consent decree, MBI is enjoined from producing and distributing drugs until the firm corrects the manufacturing violations for its eye drops and its violations of the approval and labeling requirements of the Act.

The firm's poor manufacturing conditions called into question the safety of its eye drops, and the lack of necessary warnings could have undermined the ability of a consumer to safely use the firm's pain relieving drugs listed above. FDA therefore recommended that consumers, health care providers, and caregivers dispose of the Oxydrops, Bright Eyes, Bright Eyes II, Clarity Vision for Life, Visitein, and Can-C brands of eye drops and the Biogesic, Bio-Ice, and Bio-Heat pain relieving drugs and report any adverse events related to these products to MedWatch.

The full text of FDA Press Release is available online at: http://www.fda.gov/bbs/topics/NEWS/2005/NEW01265.html.

Nationwide Recall of Triaminic Vapor Patch

Class I Recall Initiated Based on Adverse Events Associated with Swallowing Vapor Patch

On June 19, 2006, Novartis Consumer Health, in Parsippany, New Jersey, announced it was conducting a nationwide voluntary recall of all Triaminic Vapor Patch products due to the serious adverse health effects that could result if the product was ingested by a child after removing the patch and chewing on it.

Consumers who had Triaminic Vapor Patches were advised to stop using them immediately and return them to their point of purchase for a full refund or discard them. Triaminic Vapor Patches contain camphor, eucalyptus oil and menthol. Reported adverse events associated with swallowing products containing camphor or eucalyptus oils vary from minor symptoms, such as burning sensation in the mouth, headache, nausea, and vomiting, to more severe reactions such as seizures.

Triaminic Vapor Patches are labeled as cough suppressants for children 2 years of age and older. The directions on the labels indicate that the patches are to be applied externally to the throat or chest to allow the vapors to reach the nose and mouth. They are not intended for oral consumption. Multiple patches can be applied. Once applied, the patches were within reach for a child to remove and place in his/her mouth. The products were sold over-the-counter at pharmacies and retail stores nationwide.

The full text of the FDA Press Release is available online at: http://www.fda.gov/bbs/topics/NEWS/2006/NEW01392.html.

Nationwide Recall of Acetaminophen

On May 2, 2006, IVAX Pharmaceuticals, Inc., Miami, Florida, a distributor of Goldline-labeled products, initiated a recall of certain mislabeled product lots of Goldline™ brand Extra Strength Genapap 500mg (Acetaminophen) Caplets and Tablets and Extra Strength Genebs 500mg (Acetaminophen) Caplets and Tablets. Specifically, the product labels should have indicated that usage not exceed 8 tablets or caplets in a 24 hour period. This erroneous label indicated "…not to exceed 12 tablets or caplets in a 24 hour period." If a patient exceeds the maximum dosage of 8 tablets or caplets in a 24 hour period, the patient may have an **increased risk of acetaminophen toxicity to the liver**, which may cause adverse health effects. There were no reports of serious illness or injury relating to this labeling error.

Consumers who purchased mislabeled Extra Strength Genapap 500mg Caplets and Tablets or Extra Strength Genebs 500mg Caplets or Tablets were advised to cease usage and return the products to the location of purchase.

The full text of the Recall Notice with a complete list of product and lot numbers is available online at: http://www.fda.gov/oc/po/firmrecalls/ivax05_06.html.

Class I Recall: GenTeal® Gel and GenTeal® GelDrops for the Eye

Sterility Tests Reveal the Presence of Mold in Eye Drops

On November 16, 2005, Novartis Ophthalmics, East Hanover, New Jersey, announced it voluntarily recalled five lots of GenTeal® Gel and two lots of GenTeal® GelDrops, both of which are non-prescription drug products used to relieve dryness of the eye.

The GenTeal® Gel recall was conducted following concerns regarding sterility of the product manufactured for Novartis Ophthalmics by a contract manufacturer. Additional sterility tests that were conducted on several lots of GenTeal® Gel indicated the presence of mold in a small number of samples. The suspected species of mold is generally not harmful, but does have the potential to cause an eye infection in susceptible people, especially in those with compromised immune systems.

The GenTeal® GelDrops lots were recalled due to a lack of sterility assurance. While the risk of potential

contamination was believed to be very low, contaminated product could cause infections in susceptible people, and Novartis Ophthalmics initiated the recall as a precautionary measure. The sterility assurance issues were corrected. Only the two distributed GenTeal® GelDrops lots were affected.

The full text of the FDA Press Release is available online at: http://www.fda.gov/oc/po/firmrecalls/novartis211_05.html

FDA Issues Warning Regarding Drug Products for the Eye

On December 6, 2005, FDA issued a warning to consumers not to use Miracle II Neutralizer and Miracle II Neutralizer Gel products manufactured by Tedco, Inc., (Tedco) in West Monroe, Louisiana. FDA issued this warning because the products were bacterially contaminated and had not been proven to be safe and effective. Use of these products could pose a risk of serious adverse events, such as infections, particularly in children, the elderly, and individuals with weakened immune systems.

Tedco, Inc. was promoting Miracle II Neutralizer for ophthalmic use (in the eyes), including treatment of cataracts and pink eye, and as an eyewash. FDA requires that all ophthalmic products be sterile. Due to the substantial risk posed by non-sterility, Miracle II Neutralizer should never be applied to the eyes.

Tedco, Inc. was also marketing Miracle II Neutralizer for other unapproved uses, including treatment of AIDS, cancer, Crohn's Disease, dermatitis, diaper rash, diabetes, ear ache, hemorrhoids, hives, gout, herpes, mouth ulcers, psoriasis, skin cancer, and yeast infection. The firm sold Miracle II Neutralizer Gel for many of the same unapproved uses, including diaper rash, diabetes, gout, psoriasis, and skin cancer.

Tedco was promoting its Miracle II products with claims such as:

"Supreme technology has made possible a perfect soap cleaner, deodorizer, natural insecticide and antibacterial product to be put on the market. This is the only product that is made in the world that can wash a newborn baby or clean up an oil spill and everything in between."
Contrary to such claims, FDA testing of Miracle II Neutralizer and Miracle II Neutralizer Gel revealed bacterial contamination and poor manufacturing conditions.

FDA advised Tedco of the contamination found in its Miracle II Neutralizer and Miracle II Neutralizer Gel products, and the firm began a voluntary recall of these products.
A number of stores sell Miracle II Neutralizer and Miracle II Neutralizer Gel, and the products are distributed and sold worldwide and sold via the Internet. The products are packaged in

8 oz, 22 oz, and one-gallon size containers.

The full text of FDA Press Release is available at: http://www.fda.gov/bbs/topics/NEWS/2005/NEW01268.html.

Pharmacy Compounding

Seizure at Professional Compounding Centers of America

On June 15, 2006, the U.S. Marshals Service, accompanied by investigators from FDA's Dallas District Office, executed a seizure warrant at Professional Compounding Centers of America (PCCA), Houston, Texas, seizing over 300 bottles/vials, of various size, consisting of four bulk active pharmaceutical ingredients (APIs) (domperidone, polidocanol, enrofloxacin, and insulin beef powder), that were repacked by PCCA as bulk APIs intended for sale to pharmacies for use in compounding human and veterinary drug products.

Warning Letter Issued Based on FDA Concerns Regarding Health Risks Associated with Compounded Polidocanol

FDA considers the articles of drug at PCCA to be misbranded because they are intended for use in formulating finished human drugs (domperidone and polidocanol) and finished animal drugs (insulin beef powder and enrofloxacin) and their labeling does not bear adequate directions for such uses. They are not exempt from this requirement because they are intended for use in making articles that are unapproved new drugs for human use and unapproved new animal drugs.

FDA seized the domperidone and polidocanol because the agency is concerned about the public health risks associated with the compounding of drugs containing these APIs. No drugs containing these APIs are currently approved in the United States. FDA does not sanction the use of these APIs in the compounding of human drugs. FDA issued a letter to PCCA in June 2004, warning the firm to cease distributing the API domperidone and conveying FDA's public health concerns.

FDA Issues Warning Letter for Distribution of APIs for Pharmacy Compounding

On November 28, 2005, FDA's New Jersey District Office issued a Warning Letter to the Chief Executive Officer of Spectrum Chemicals and Laboratory Products, Inc. (Spectrum Chemicals) Tucson, Arizona, after an FDA inspection of the firm's New

Brunswick, New Jersey facility revealed that the firm received active pharmaceutical ingredients (APIs), including polidocanol, from manufacturers and distributors and repackaged and relabeled them for distribution to pharmacies for compounding. FDA is very concerned about the public health risks associated with compounded polidocanol. Polidocanol is not an active ingredient contained in any FDA-approved drug product. FDA does not sanction its use in pharmacy compounding.

FDA considered the articles of drug at Spectrum Chemicals to be misbranded because they are intended for use in formulating finished human drugs and their labeling does not bear adequate directions for such uses. They are not exempt from this requirement because they are intended for use in making articles that are unapproved new drugs.

FDA Inspection Finds Significant Violations of CGMPs in Manufacture of 13 Injectable Drug Products

Furthermore, the list of APIs produced during the inspection indicated that Spectrum Chemicals was distributing adenosine-5-monophosphate to pharmacies for compounding. Drugs containing adenosine-5-monophosphate were removed from the market in 1973, for safety reasons.

Spectrum Chemicals was warned in June of 2004 that the firm may not distribute APIs for compounding that are not components of approved drugs. That Warning Letter was based on the firm's distribution of the API domperidone for use in compounding human drugs. The firm was advised that domperidone was not a component of an FDA-approved drug and the agency does not tolerate its distribution for human drug compounding. The November 2005 Warning Letter noted that the fact that the firm continued this practice is extremely troubling.

The full text of the Warning Letter is available online at: http://www.fda.gov/foi/warning_letters/g5649d.htm.

Warning Letter Issued to Pharmacy Compounding Firm

On February 15, 2006, FDA's New Orleans District Office issued a Warning Letter to the President and Owner of Southern Meds Joint Venture, LLC (Southern Meds), Biloxi, Mississippi. On August 3-5 and 11, 2005, an FDA investigator inspected the Southern Meds facility, located in Biloxi, Mississippi, and documented serious violations of the FD&C Act.

FDA's inspection revealed that the firm manufactures thirteen injectable drug products, eight of which had the same strength as other commercially available products.

The Warning Letter noted that, "For the purpose of the agency's exercise of its enforcement discretion, the availability of different size vials are not a meaningful distinction between your products and the commercially available products. Further, FDA found no documentation of the medical need for the variation between solutions and suspensions.'

The Warning Letter also noted that FDA does not believe the firm's production volume is consistent with that of a traditional pharmacy compounding operation.

In addition, the inspection found significant violations of the current good manufacturing practice (CGMP) regulations for a drug product. The CGMP violations included, but were not limited to, the following:

- Failure to establish and follow appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile;
- Failure to have control systems to prevent contamination;
- Failure to have written standards or specifications and methods of testing to remove pyrogenic properties;
- Failure to test each batch of drug product purporting to be sterile by appropriate laboratory determination of satisfactory conformance to final specifications; and,
- Failure to prepare and maintain batch production and control for each batch of prescription injectable drug product produced by this firm.

The full text of the Warning Letter is available online at: http://www.fda.gov/foi/warning_letters/g5719d.htm.

FDA Warns Three Pharmacies to Stop Mass-Producing Unapproved Inhalation Drugs

Compounding Mass Amounts of Inhalation Drugs Extends Well Beyond Traditional Pharmacy Compounding

On August 9, 2006, FDA warned three firms, RoTech Healthcare, Inc., CCS Medical, and Reliant Pharmacy Services to stop their manufacturing and nationwide distribution of thousands of doses of compounded, unapproved inhalation drugs.

The three firms claimed that they produce inhalation drugs as part of the practice of pharmacy compounding. However, traditional pharmacy compounding typically involves drugs

that are **not commercially available**, such as a unique medicine for a patient who is allergic to an ingredient in an FDA-approved drug. This kind of compounding follows a physician's decision that his or her patient has a special medical need that cannot be met by FDA-approved drugs.

FDA normally permits traditional pharmacy compounding and is not targeting this practice.

The three firms were making inhalation drugs that are used to treat diseases including asthma, emphysema, bronchitis, and cystic fibrosis. These are potentially life-threatening conditions for which numerous FDA-approved drugs are available.

FDA noted in a Press Release dated August 10, 2006, that these compounded inhalation drugs may be distributed to patients in multiple states, and patients and their doctors may not know that they are receiving compounded products. FDA urged consumers using inhalation drugs to discuss their medications with their physicians and verify with their pharmacists that the medications they received are what their physicians ordered.

FDA believes that, in compounding mass amounts of inhalation drugs, a number of pharmacies go well beyond traditional compounding. FDA is aware of certain pharmacies compounding millions of doses of inhalation drugs per year.

The full text of the Warning Letter to Rotech Healthcare, Inc., Orlando, Florida is available online at: http://www.fda.gov/foi/warning_letters/g5964d.htm.

The full text of the Warning Letter to CCS Medical, Clearwater, Florida is available online at: http://www.fda.gov/foi/warning_letters/g5963d.htm.

Post Marketing Surveillance Programs

Post Marketing Adverse Event Reporting

Drug safety reporting regulations apply to adverse events associated with the use of prescription drugs and the use of over-the-counter drugs with approved applications. Firms holding approved applications for prescription and OTC drugs, and firms whose names appear on the label as manufacturers, packers or distributors of prescription drugs and OTC drugs with FDA approved applications are required by federal regulations (See 21 CFR §§ 310.305, 314.80, 314.98, 600.80, and 600.81) to submit adverse drug experience reports to FDA. Firms that have FDA approvals for their drug products are required to report even if the drug is not marketed in the United

States.

FDA monitors the pharmaceutical industry's submission of adverse drug experience (ADE) reports. A firm's procedures for collection, evaluation and submission of adverse drug experience information may affect the quality and completeness of safety data available to FDA for analysis.

Risk-Based Inspections

FDA's surveillance of industry is based upon the risks associated with specific drug products and specific data processing procedures. FDA inspects drug firms' adverse drug experience reporting based upon risk criteria associated with specific drug products and corporate performance. These include:

- Newly marketed drugs
- Emerging safety signals
- Previous violations
- Corporate transitions

Outreach and Education

In addition to the inspectional program for adverse drug experience reporting compliance, FDA improves safety reporting through educational presentations to industry and FDA personnel. FDA's educational activities include formal presentations at global industry meetings such as the Food and Drug Law Institute, Pharmaceutical Educational and Research Institute, American Society for Quality, and the Drug Information Association.

FDA's educational outreach also extends to training field investigators at Basic Drug School on Postmarketing ADE Reporting Regulations and how to conduct an ADE inspection and training for FDA field investigators on pharmacovigilance.

Inspection Outcome

In cases where firms' non-compliance did not have significant impact on product safety, FDA worked to educate industry on regulatory requirements and to monitor the adequacy of corrective actions undertaken by firms in response to inspection. However, in cases where a firm had significant violations and did not make sufficient corrective actions, a warning letter was issued to the firm.

FDA receives reports of drug quality issues (See Figure 1). The drug quality problems range from quality issues related to a drug delivery system failure to issues that may be associated with bioequivalence or formulation (See Figure 2). Most of these reports are received through the Agency's Medwatch Program, which is the sole source for voluntary data reporting for health professionals and consumers. These drug quality reports are shared with the firm whose products are involved and with the

FDA District in which the firm resides. FDA evaluates and prioritizes these drug quality reports for follow-up actions. Follow-up actions may include routine follow-up by the District at the next scheduled inspection or an assigned inspection. Many enforcement actions taken by the Districts are the direct result of actions that were initiated by the receipt of a drug quality report. In addition to District follow-up, these reports may result in a recall, or a public health alert.

CDER's Office of Compliance Division of Compliance Risk Management and Surveillance received a Drug Quality Reporting System (DQRS) report from an ophthalmologist that several patients had experienced adverse events after using Cytosol's balanced salt solution during surgery. Investigation of the reported problem revealed that the product was contaminated with endotoxins causing a serious and potentially irreversible eye injury called Toxic Anterior Segment Syndrome (TASS) resulting in the recall of the product.

In May 2005, The DQRS Program received a MedWatch report concerning possible quality issues with Transdermal Fentanyl Patches. A CGMP inspection at the manufacturing facility was initiated that included an inspectional review of production, and testing records for the suspect lot. As a result of the inspection and sample analysis, it was determined that the patches met all manufacturing and analytical specifications.

NDA Field Alert Reporting System

Additionally, holders of New and Abbreviated New Drug Applications are required to submit to the FDA a Field Alert Report (FAR) for any incident that involves mislabeling, a bacterial contamination, any significant change or deterioration, or a failure of a distributed batch of drug to meet specifications (21 CFR 314.81). These reports are sent to the District Office that is responsible for the facility. The reports are sent to CDER by the district for further review and analysis. If significant trends or issues are identified, then CDER works with the District Office to initiate and coordinate subsequent follow-up actions. These reports may result in a number of outcomes including a recall, changes in the firm's standard operating procedures or formulation, or submission of a supplement to the firm's application.

Examples of outcomes from FARs
These reports may be made by the firm in conjunction with a recall or subsequent investigation, and may result in a number of outcomes, including changing a firm's standard operating procedure, changing a drug formulation, or revising laboratory methodology. Pliva Inc. submitted a field alert stating that their theophylline extended release 450 mg tablets, lot 5185001SB, failed to comply with their dissolution specifications during the 6 month stability testing. The firm subsequently recalled the lot.

A generic drug manufacturer reported through the NDA Field Alert Reporting System that the initial test for EDTA at 24 months was below the product's specification. The firm determined that their EDTA limit was set too high and subsequently submitted a changes-being-effected-in-30-days supplement (CBE-30)

to FDA, which was granted.

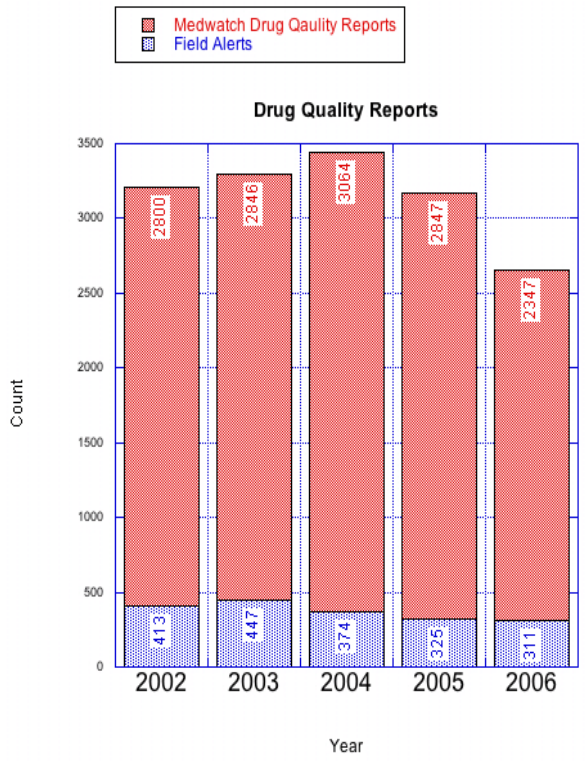


Figure 1. DQRS reports received by year.

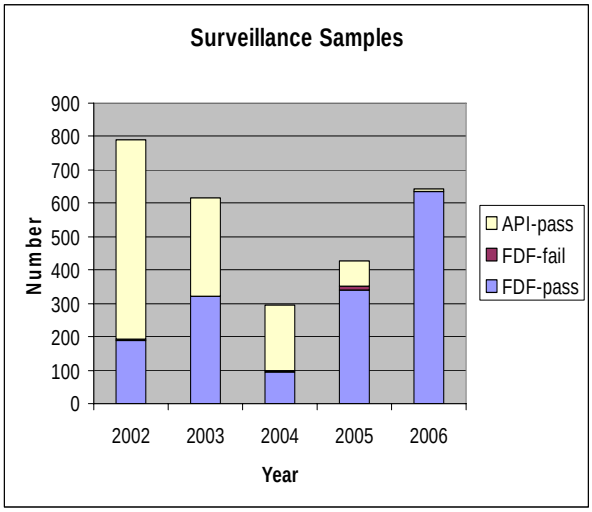
DEFECT	COUNT
FORMULATION QUESTIONED	365.00
DISPENSE DEVICE MALFUNCTION	170.00
GENERIC SUBSTITUTION QUESTIONED	156.00
POTENCY QUESTIONED	123.00
ADHESION LACKING	98.00
PATIENT REACTION	89.00
DOSAGE UNITS MISSING	85.00
CONTROLLED DOSAGE UNITS MISSING	82.00
FRIABILITY POOR	77.00
MIXUP WITHIN PRODUCT	77.00

Figure 2. Top 10 DQRS defects reported in FY2006.

Drug Survey Program

FDA conducts post market drug product surveys to assess the quality of the nation's drug supply through risk-based sampling and analysis of marketed drug products. The program detects marketed products with drug quality issues, but also very importantly, it provides some assurance that the drugs marketed in the United States are safe. The program additionally identifies emerging methodology problems, maintains analytical expertise, and has a watchdog effect. The selection of drug survey products is based on established risk criteria which target products that pose the highest risk to consumers.

FDA surveys both domestic and foreign finished drug products (finished dosage forms, FDF) and active pharmaceutical ingredients (APIs). The Agency's district laboratories analyze the targeted products for conformity with applications, compendial standards, or manufacturer's specifications. The agency uses the survey results to help in their risk-based inspection and enforcement decisions.



API – Active Pharmaceutical Ingredients
FDF – Finished Dosage Form

Figure 3. Five-Year Surveillance Samples

FDA Announces New Measures to Protect Americans from Counterfeit Drugs

On June 9, 2006, FDA announced new steps to strengthen existing protections against the growing problem of counterfeit drugs. The measures, which were recommended in a report released by the agency's Counterfeit Drug Task Force, emphasized certain regulatory actions and the use of new technologies for safeguarding the integrity of the U.S. drug supply.

Among other new measures, FDA will fully implement regulations related to the Prescription Drug Marketing Act of 1987, which requires drug distributors to provide documentation of the chain of custody of prescription drug products -- the so-called "pedigree" -- throughout the distribution system.

In early 2004, FDA placed the effective date of the regulatory provisions regarding pedigrees on hold to allow the industry time to adopt new electronic track and trace technology, such as radio-frequency identification (RFID), which creates an electronic pedigree (e-pedigree) for tracking the movement of the drug through the supply chain. Based on information from drug supply stakeholders, FDA had expected this technology to be in widespread use in the drug supply chain by 2007, but these expectations had not been met.

Nevertheless, during a public workshop held in February 2006, most drug stakeholders encouraged FDA to allow the hold to expire. Doing so would provide clarity in the drug supply chain regarding who is required to provide a pedigree. Continuing the

hold would have perpetuated the current confusion and allowed further opportunities for counterfeit and diversionary practices. FDA therefore determined that it must allow the hold on the effective date of the pedigree requirements to expire in December.

Consistent with recommendations of the Task Force, FDA also announced in the *Federal Register* the availability of a draft compliance policy guide describing how, during the next year, its enforcement of the pedigree regulations will focus on products most susceptible to counterfeiting and diversion. FDA may, under appropriate circumstances, initiate regulatory action, including criminal prosecution, for pedigree violations that do not meet the factors listed in the guidance. By providing guidance on the types of drugs that are currently of greatest concern to FDA, the agency intends to give wholesale distributors a better idea of where and how to focus their initial energies to come into compliance with the regulations (21 CFR Part 203) for prescription drugs they distribute.

The Task Force report also underlined the agency's belief that widespread use of e-pedigrees using electronic track and trace technology, including RFID, would provide an electronic safety net for our nation's drug supply. The report therefore recommended that stakeholders continue to work expeditiously toward that goal, and that their implementation of RFID technology be used first on products most susceptible to counterfeiting and diversion.

The June 2006 Task Force report is the third in a series of documents exploring the means of ensuring the safety of the U.S. drug supply. The first report, issued in 2004, outlined the framework for protecting the public from counterfeit medicines, and the second report, released last year, assessed the progress toward implementing the 2004 recommendations. All Task Force Reports are posted on FDA's Web at www.fda.gov/counterfeit .

Update: On December 8, 2006, a federal district court in the Eastern District of New York issued a preliminary injunction in *RxUSA Wholesalers, Inc. v. HHS* to prohibit FDA from implementing a regulation that requires that certain information be included in a pedigree, which documents the custody of certain prescription drugs in the drug supply chain. The regulation, [21 CFR 203.50(a)] which went into effect on December 1, 2006, was issued by FDA to implement the Prescription Drug Marketing Act of 1987, as amended by the Prescription Drug Amendments of 1992 (PDA).

FDA continues to believe that its regulation faithfully interprets the Federal Food, Drug, and Cosmetic Act (specifically, the PDMA and the PDA) and intends to defend both the regulation and the statute as the litigation continues.

Additional information is available in FDA's "Backgrounder re: RxUSA Wholesalers, Inc. v. HHS." To view the full text of the "Backgrounder" go to: http://www.fda.gov/cder/regulatory/PDMA/PDMA_backgrounder.pdf.

Warning Letter Issued to Firm For Deviations from ADE Requirements

On August 15, 2006, FDA's New Jersey District issued a Warning Letter to the President of Actavis Towa, LLC, Little Falls, New Jersey. FDA conducted an inspection of the firm from January 10–February 8, 2006. FDA's inspection was conducted to determine the firm's compliance with the post marketing adverse drug experience (ADE) reporting requirements of the FD&C Act.

The following deviations from the ADE reporting requirements included, but were not limited, to the following:

- Failure to submit to FDA ADE reports dating back to 1999;
- Failure to promptly investigate serious and unexpected ADE reports;
- Failure to adequately review ADE Information;
- Failure to submit periodic safety reports as required by FDA regulations; and
- Failure to develop procedures for the surveillance, receipt, evaluation and reporting of adverse events.

Promotional Claims/Labeling

Pharmaceutical Firm Receives Warning for Misleading Claims and Omitting Risk Information

FDA Finds Drug Ad Minimizes Risks Associated with Cenestin

On January 6, 2006, CDER's Division of Drug Marketing, Advertising, and Communications (DDMAC) issued a Warning Letter to the President and Chief Operating Officer of Duramed Pharmaceuticals, Inc., (Duramed), located in Bala Cynwyd, Pennsylvania. The Warning Letter stated that CDER had reviewed a professional journal advertisement (ad) for Cenestin (synthetic conjugated estrogens, A) Tablets, submitted by Duramed Pharmaceuticals, Inc.

The Warning Letter advised the firm that FDA considered the ad both false and misleading because the advertisement:

- Omitted material risk information;
- Minimized the risks associated with Cenestin therapy; and
- Presented unsubstantiated implied superiority claims.

The Warning Letter noted that the ad was misleading because it suggested, among other things, that:

- Cenestin is superior to other estrogen formulations (patch or tablet). This has not been demonstrated by substantial evidence or substantial clinical experience;

- Cenestin offers distinct patient benefits, because of "consistent estrogen release." However, FDA is not aware of any studies demonstrating that the absorption and dissolution characteristics of Cenestin offer any distinct patient benefits or that the consistent release of hormone over time conveys any clinically significant advantage;

- Cenestin "offers distinct patient benefits" because it is available in a low 0.45 mg dose. However, at least one drug for the treatment of moderate to severe vasomotor symptoms associated with menopause is available in a lower starting dose (0.3 mg).

The Warning Letter requested that Duramed immediately cease the dissemination of violative promotional materials for Cenestin such as those described above.

The full text of the Warning Letter is available online at: http://www.fda.gov/foi/warning_letters/g5688d.htm

Warning Letter Issued for False and Misleading Promotional Mailer

On February 1, 2006, CDER's Division of Drug Marketing, Advertising, and Communications (DDMAC) issued a Warning Letter to the Chief Executive Officer and Managing Director of Mayne Pharma (USA), Inc., located in Paramus, New Jersey, regarding M.V.I.-12 (Multi-Vitamin Infusion without vitamin K). The Warning Letter stated that CDER had reviewed a promotional mailer for M.V.I.-12 submitted by Mayne Pharma (USA), Inc. (Mayne).

The Warning Letter advised the firm that the promotional mailer was false or misleading because it omitted important risk information for M.V.I.-12. Therefore, the drug was misbranded in violation of the Federal Food, Drug, and Cosmetic Act (the Act).

The FDA-approved Promotional Information contains important contraindications, warnings, precautions, and adverse reactions.

The Warning Letter noted that the Promotional Mailer omitted this Risk Information.

The Warning Letter stated [in part] the following:

"The promotional mailer includes a reference to the full prescribing information. This statement, however, **is**

not sufficient to provide appropriate qualification or pertinent information for claims made in the mailer. For the piece to be truthful and non-misleading, it must contain risk information in each part as necessary to qualify any safety or effectiveness claims made in that part. Because the piece makes effectiveness claims but contain no risk information, it is false or misleading."

The Warning Letter stated that because promotional mailer omitted important risk information about M.V.I.-12 and the drug is misbranded in violation of the Act.

CDER's DDMAC requested that Mayne:

- Immediately cease the dissemination of violative promotional materials for M.V.I.-12 such as those described above;
- Submit a written response to FDA's letter on or before February 15, 2006, stating whether the firm intends to comply with FDA's request, listing all violative promotional materials for M.V.I.-12 such as those described above, and explaining the firm's plan for discontinuing use of such materials; and,
- Include a comprehensive plan of action to disseminate truthful, non- misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials.

The full text of the Warning Letter is available online at: http://www.fda.gov/foi/warning_letters/g5705d.htm.

Unapproved New Drugs

Seizure at Allegheny Cold Storage, Co., Inc.

On April 15, 2006, at the request of FDA, the U.S. Marshal's Service seized dried hyper-immune egg products located at Allegheny Cold Storage, Co., Inc., in Pittsburgh, Pennsylvania. The seized articles were in violation of the new drug and misbranding provisions of the FD&C Act, 21 U.S.C. 355(a), 352(f)(1), and 352(o).

The owners of the seized goods and OvImmune, Inc., Richwood, Ohio, were previously convicted in criminal court of violations related to their manufacture and sale of the hyper-immune egg products.

The seized articles are powdered egg products, with claims for their efficacy in treating numerous human diseases, including (but not limited to) rheumatoid arthritis, vaginitis, attention deficit disorder, fibromyalgia, chronic fatigue syndrome, and toenail fungus. These claims were made on OvImmune's Website, in its Articles of Incorporation,

on patient consent forms, and orally to customers.

FDA Issues Warning Letters for Unapproved New Drugs to Treat ED

In July 2006, FDA issued Warning Letters to six firms that promoted products as dietary supplements intended for sexual enhancement and for the treatment of erectile dysfunction. FDA laboratory analysis of each of the products listed in the table below determined that they contained either sildenafil or an analogue of sildenafil or vardenafil. Sildenafil and vardenafil are the active pharmaceutical ingredients in the drugs Viagra and Levitra, respectively, which are approved by FDA for the treatment of erectile dysfunction.

By way of example, one of the Warning Letters was issued to Herbn Tonics, LLC, Beverly Hills, California for the product Nasutra. The Warning Letter noted the following:

"Under 21 U.S.C. 321(g)(1), the structure/function claims made for a dietary supplement must be made in accordance with 21 U.S.C. § 343(r)(6), or the product is subject to regulation as a drug. Title 21 U.S.C. § 343(r)(6) authorizes claims that describe the role of a nutrient or dietary ingredient intended to affect the structure or function of the body, or characterize the way in which a nutrient or dietary ingredient maintains the structure or function of the body. In the case of Nasutra, however, the sexual performance structure/function claims do not describe the effects of nutrients or dietary ingredients in the product.

Rather, these claims are made for the product as a whole and relate to its acetildenafil content. Since acetildenafil is not a nutrient or dietary ingredient but a synthetic analogue of sildenafil, the claims about improvement of sexual function do not conform to 21 U.S.C. § 343(r)(6). Accordingly, Nasutra is a drug within the meaning of section 201(g)(1)(C).

Moreover, this product is a new drug, as defined by 21 U.S.C. § 321(p), because it is not generally recognized as safe and effective for its labeled uses.

Under 21 U.S.C. §§ 331(d) and 355(a), a new drug may not be introduced or delivered for introduction into interstate commerce unless an FDA-approved application is in effect for it. The sale of Nasutra without such an approved application violates these provisions of the Act.

Additionally, the product labeling does not declare that the product contains acetildenafil. Further, the website states

that Nasutra "has none of the negative side effects of other erection products on the market" and "has no known interactions with any medications or dietary supplements" even though acetildenafil likely exhibits similar pharmacological action to sildenafil.

Furthermore, because this product is offered for conditions that are not amenable to self-diagnosis and treatment by individuals who are not medical practitioners, adequate directions cannot be written so that a layman can use this product safely for its intended uses. Thus Nasutra's labeling fails to bear adequate directions for its intended uses, causing it to be misbranded under 21 U.S.C. § 352(f)(1). Finally, the product is also misbranded under 21 U.S.C. § 352(f)(2), because the labeling lacks adequate warnings for the protection of users."

These statements falsely assert that the product does not have the potential to cause side effects. These statements and the failure to disclose the presence of acetildenafil renders this product's labeling false and misleading. Nasutra is therefore misbranded under 21 U.S.C. § 352(a).

The press release that describes these actions is available at **http://www.fda.gov/bbs/topics/NEWS/2006/NEW01409.html**.

Warning Letter Issued for Misbranded Oxygen

BetterthanAir Labeling Promotes Product to Treat Aids, Lung Cancer, Cystic Fibrosis, Among Other Diseases

On July 21, 2006, FDA's Denver District Office issued a Warning Letter to the General Manager, BetterthanAir, LLC, Evergreen, Colorado. The Warning Letter stated that, based on labeling claims on the firm's website, BetterthanAir oxygen products are intended to treat, prevent, and mitigate disease and/or affect the structure or function of the body and are, therefore, drugs. The Warning Letter noted that statements on the firm's website promoted these oxygen products to treat:

- "AIDS,
- Lung Cancer,
- Chronic Mountain Sickness,
- High Altitude Sickness (HAPE),
- Interstitial Lung Disease,
- Cystic Fibrosis,
- Sequelae Tuberculosis,
- Bronchiectasis,
- Kyphoscoliosis,
- Neuromuscular Diseases,
- Sleep Apnea Syndromes,

- Primary Hypoventilation Syndromes, and Pulmonary Hypertension,"

Other website statements that demonstrate the intended use of the BetterthanAir oxygen products as drugs include:

- "Oxygen deprivation can, and is believed by the Medical Society to cause life-threatening diseases such as cancer."

- As stated in the Warning Letter, "BetterThanAir oxygen enriched products" are new drugs because they are not generally recognized as safe and effective for the intended uses.

  Because the firm has no approved applications for these new drugs, it markets them in violation of the Act. Furthermore, these products are misbranded because their labeling fails to bear adequate directions for use.

The full text of the letter is available at: http://www.fda.gov/foi/warning_letters/g5951d.htm

Warning Letters Issued to Firms Marketing 35% Hydrogen Peroxide

DFWX's Website Misleadingly States "...it is believed that hydrogen peroxide may help prevent and even combat cancer."

On July 19, 2006, FDA's Dallas District Office in collaboration with CDER issued Warning Letters to two firms that were illegally marketing 35% Hydrogen Peroxide. The Warning Letters were issued to Frad 35, Inc., Clyde, Texas, and DFWX, 301 W. Witt, Wolfe City, Texas. Frad 35, Inc., and DFWX marketed the product 35% Hydrogen Peroxide on their websites, www.h2o2-4u.com and www.dfwx/h2o2.com/htm, respectively.

The Warning Letter issued to Frad 35 Inc., noted that statements on the firm's website, and in documents linked to the website, state that the intended uses of the product include, but are not limited to, the following:

- "Intravenous hydrogen peroxide rapidly relieves allergic reactions, influenza symptoms, and acute viral infections."

- "Tumor cells, bacteria, and other unwanted foreign elements in the blood can usually be destroyed with hydrogen peroxide treatment. Peroxide has a definite destructive effect on tumors, and, in fact, cancer

therapy may prove to be the most dramatic and useful place for peroxide therapy. . .."

The Warning Letter issued to DFWX noted that statements on the firm's website state that the intended uses of the product include, but are not limited to, the following:

- "Thus, it is believed that hydrogen peroxide may help prevent and even combat cancer."

- "Conditions which can be treated with H_2O_2 [hydrogen peroxide] include those conditions which can be treated with antibiotics, but without the serious toxicity often associated with laboratory produced synthetic antibiotics. Some of these conditions are candidiasis (yeast), viral infections, influenza, the common cold, sinus infection, Epstein-Barr virus and gangrene."

- "Hydrogen peroxide also has been found to dissolve cholesterol and calcium deposits associated with atherosclerosis. Therefore, it is a good treatment for vascular disorders. This can result in lessening or disappearance of angina . . . can help reverse some of the damage left over by a stroke . . . ."

- "Some doctors believe AIDS and cancer can be helped with hydrogen peroxide."

- "It also clears the lungs, in cases of emphysema . . . ."

- "In addition, hydrogen peroxide benefits asthma, leukemia, multiple sclerosis, degenerative spinal disc disease and high blood pressure. It is particularly effective with asthma, arthritis and back disorders."

The Warning Letters stated that *35% Hydrogen Peroxide* is a drug because it is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. Moreover, this product is a new drug, because it is not generally recognized as safe and effective for its labeled uses. Under the Act, a new drug may not be introduced or delivered for introduction into interstate commerce unless it has an FDA-approved application. The firms' sale of *35% Hydrogen Peroxide* without an approved application violates the FD&C Act.

The Warning Letters also stated that the product is misbranded because its labeling fails to bear adequate directions for its intended uses. Additionally, the Warning Letter to Frad 35, Inc., also stated that *35% Hydrogen Peroxide* is dangerous to health when used in the dosage or manner or with the frequency or duration prescribed, recommended, or suggested in the product's labeling. For example, hydrogen peroxide taken orally can cause severe gastrointestinal

irritation leading to ulceration, and IV administration may result in vaculitis and potentially life-threatening allergic reactions.

The full text of the Warning Letters are available online at: http://www.fda.gov/foi/warning_letters/g5943d.htm.

FDA Warns Consumers Against Drinking High-Strength Hydrogen Peroxide for Medicinal Use

FDA Warns that "35 Percent Food Grade Hydrogen Peroxide" Can Cause Serious Harm Including Death When Ingested

On July 27, 2006, FDA issued a warning to consumers not to purchase or use 35% hydrogen peroxide products, including a product marketed as "*35 Percent Food Grade Hydrogen Peroxide,*" for medicinal purposes. FDA recommended that consumers who were currently using high-strength hydrogen peroxide stop immediately and consult their health care provider.

FDA continues to work to stop companies selling high-strength hydrogen peroxide from making illegal medical claims about their products. These claims are illegal because these products do not have FDA approval and are therefore being sold illegally for medical indications without any proven clinical value. As part of these ongoing efforts, FDA issued Warning Letters to two firms illegally selling "35 percent hydrogen peroxide" products on websites for the treatment of AIDS, cancer, emphysema, and other serious and life-threatening diseases.

FDA has never approved high-strength hydrogen peroxide to be taken internally and considers hydrogen peroxide at 35 percent strength to be dangerous, even if handled according to the manufacturer's directions. This strength of hydrogen peroxide -- more than 10 times stronger than the solution used in over-the-counter drugs to disinfect minor cuts -- is highly corrosive.

Ingestion of hydrogen peroxide can cause gastrointestinal irritation or ulceration. Intravenous administration of hydrogen peroxide can cause inflammation of the blood vessel at the injection site, gas embolisms (bubbles in blood vessels), and potentially life-threatening allergic reactions.

The full text of the Press Release is available online at: http://www.fda.gov/bbs/topics/NEWS/2006/NEW01420.html.

FDA Strengthens its Efforts Against Unapproved Drug Products

FDA Estimates that 2% of Prescribed Drugs are Unapproved

On June 8, 2006, FDA announced that it was strengthening its efforts against unapproved drug products. FDA estimates that there are several hundred different unapproved active ingredients in prescription drugs on the market. The agency estimates that less than 2 percent of prescribed drugs are unapproved.

The agency issued a final guidance document outlining its approach to addressing drugs that are marketed without FDA approval. The guidance document is titled Compliance Policy Guide Sec. 440.100 Marketed New Drugs Without Approved NDAs or ANDAs.

The first action under the new guidance concerns carbinoxamine-containing products. Carbinoxamine-containing products require FDA approval to be marketed, but numerous products containing carbinoxamine, either alone or in combination with other active ingredients, are marketed without FDA approval. To date, FDA has approved two carbinoxamine products for various allergic symptoms.

Many unapproved carbinoxamine products are labeled for treatment of cough and cold symptoms, an indication for which carbinoxamine has not been found safe and effective by FDA. Various companies sell carbinoxamine drops and syrups that are specifically labeled for use in children as young as one month of age. Carbinoxamine has never been studied in very young children, and FDA cannot predict how they will respond to it. However, children under 2 years of age are more susceptible to drug-related adverse events, in part due to the immaturity of their systems.

Many of the unapproved drugs affected by the guidance document, Compliance Policy Guide Sec. 440.100 Marketed New Drugs Without Approved NDAs or ANDAs are medicines that were developed and marketed before successive changes to the drug approval process that is established in the Federal Food, Drug, and Cosmetic Act. Today, FDA approval guarantees that a product has been reviewed and will be consistently monitored for safety, effectiveness and adherence with manufacturing quality standards.

Under the new guidance, FDA is encouraging companies to comply with the drug approval process and seek approval for their products, as well as safeguarding consumer access to important medicines. The guidance identifies as the highest priority for agency enforcement action those unapproved products that are most likely to pose a risk to public health. The guidance explains that FDA intends to continue to give priority to enforcement actions involving unapproved drugs (1) with potential safety risks, (2) that lack evidence of effectiveness, and (3) that constitute health fraud.

The guidance also explains how the agency intends to address those situations in which a company obtains FDA approval to sell a drug that other companies have long been selling without FDA approval. Those manufacturers that do not comply with drug approval requirements may be subject to enforcement action.

Additional information can be found on FDA's Unapproved Drugs Web Page, available online at http://www.fda.gov/cder/drug/unapproved_drugs/default.htm